This is borne out by the reissue Declaration which states factually the results of the mass spectral analysis and the proposed mechanism by which the compound of the present invention has been formed.

In this connection, the rejection raised by the Examiner under 35 USC 251 as concerns the claims as noted in paragraph 2 of part 3 of the Official Action is also respectfully traversed, in that the material contained in said reissue Declaration is indeed factual and adequately shows the reasoning resulting in the present reissue application.

Applicants claim priority under 35 USC 119 based upon French Patent Application Number 72 07 647, filed March 6, 1972 in order to obviate the rejection raised by the Examiner in paragraph 3 of part III of the Official Action. This also attends to the first part of paragraph 5 of part III of the Official Action.

In conformance with the Examiner's request in the other part of paragraph 5 of the Official Action, applicants enclose the original Letters Patent in conformity with MPEP 1401.041.

Applicants believe the present application is allowable. However, we would sincerely appreciate the Examiner's comments by telephone if further clarification is required.

Respectfully submitted,

Michael N. Meller

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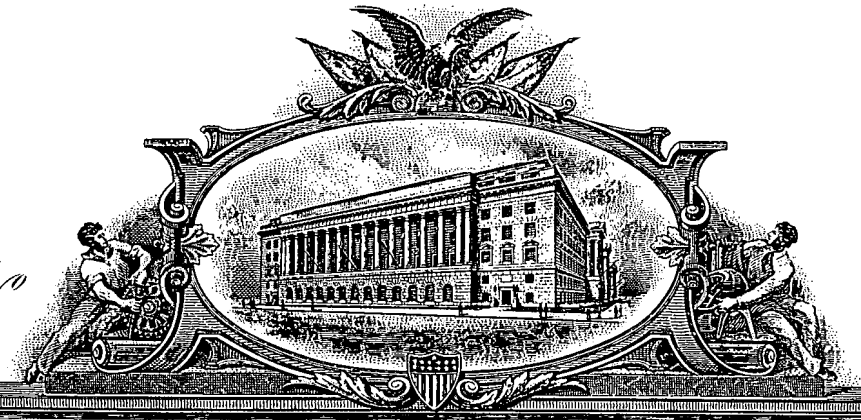
MK:sb

Enclosure:
Letters Patent

2496 us



No. 3962238

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE

Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATIONS OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE Letters Patent ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE [illegible]RS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE [illegible]D STATES.

In testimony whereof *I have hereunto set my hand and caused the seal of the* **Patent and Trademark Office** *to be affixed at the City of Washington this* eighth *day of* June *in the year of our Lord one thousand nine hundred and* seventy-sixth, *and of the Independence of the United States of America the two hundredth*

Attest:

Ruth C. Mason

United States Patent [19]
Mauvernay et al.

[11] 3,962,238
[45] June 8, 1976

[54] **ETHERS OF N-PROPANOL AMINE**

[75] Inventors: **Roland Yves Mauvernay**, Riom; **Norbert Busch**, Loubeyrat; **Jacques Moleyre**, Mozac; **André Monteil**, Gerzat; **Jacques Simond**, Chamalieres, all of France

[73] Assignee: **Centre Europeen de Recherches Mauvernay "CERM"**, Riom, France

[22] Filed: **Feb. 27, 1973**

[21] Appl. No.: **336,357**

[30] **Foreign Application Priority Data**

Mar. 6, 1972 France 72.07647

[52] **U.S. Cl.** ..... **260/247.2 B;** 260/247.5 R; 260/293.79; 260/296 AE; 260/326.5 L; 260/326.5 R; 260/570.6; 260/570.9; 260/573; 424/248; 424/267; 424/274; 424/325

[51] **Int. Cl.²** **C07D 295/00**

[58] **Field of Search** ..... 260/326.5 L, 247.2 B, 260/247.5 R, 293.76, 296 AE, 570.9, 570.6, 573

[56] **References Cited**

UNITED STATES PATENTS

2,600,301	6/1952	Kerwin	260/570.9
2,832,795	4/1958	Hempel et al.	260/570.9
3,666,811	5/1972	Van der Steldt	260/570.9

Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Haseltine, Lake & Waters

[57] **ABSTRACT**

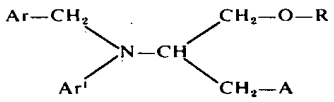
Ethers of n-propanolamine, preparation thereof and their use in treatment of cardiovascular conditions.

6 Claims, No Drawings

ETHERS OF N-PROPANOL AMINE

This invention relates to ethers of n-propanolamine, to the preparation thereof and to the use thereof.

The present invention provides an ether of an n-propanolamine having the general formula:



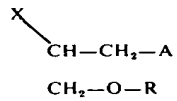
(I)

in which A is a tertiary aliphatic, cycloaliphatic or heterocyclic amino group, R is a straight or branched chain lower alkyl group or an aralkyl group, Ar is an aromatic group and Ar^1 is an aromatic or heterocyclic group, and addition salts thereof with pharmacologically acceptable acids.

When Ar and Ar^1 are both aromatic groups they may be like or unlike. Ar and Ar^1 may both be monocyclic aromatic groups and Ar^1 may be a heteromonocyclic group which may contain a nuclear nitrogen atom with or without an additional nuclear hetero atom.

The compounds of the present invention are useful as medicaments especially in the treatment of cardiovascular conditions.

In earlier patent applications we have described compounds having the general formula:

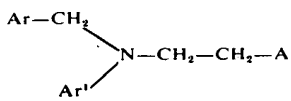


(II)

in which A and R have substantially the same meanings as in formula I above, and X respectively represents the following groupings in the various cases:

—O—CO—Ar	French Special Medicine Patent No. 6571 M - 352 CAM
—N—CO—Ar H	French Special Medicine Patent No. 7700 M
OH —C Ar Ar¹	French Patent No. 70/00018
H —C Ar Ar¹	French Patent No. 69/24645

Moreover, compounds having the following general formula are already known for their properties as antihistamines:

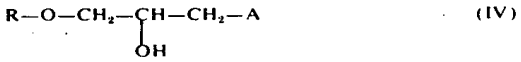


(III)

in which A has the same meaning as in the general formulae I and II above, whilst Ar and Ar^1 are aromatic groups. (Ehrhart/Ruschig Arzneimittel I, pages 208–210).

The compounds according to the present invention having the general formula I, are manifestly different from any of these groups of compounds.

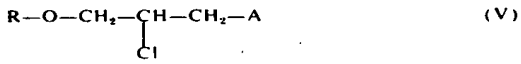
The compounds of the present invention may be prepared from amino alcohols having the general formula:



(IV)

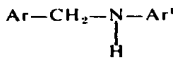
in which A and R are as defined above in connection with formula I.

In the first step of such preparation, the amino alcohols (IV), which are known materials, and are described inter alia in Belgium Pat. No. 718 425, are treated with thionyl chloride dissolved in a suitable solvent such as chloroform in order to obtain the corresponding chloro compounds having the general formula:



(V)

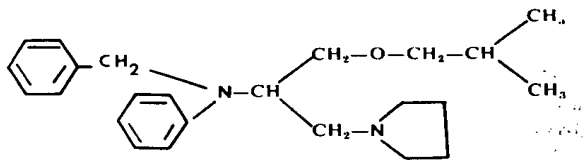
The latter compounds are then condensed with amines having the general formula



which have previously been converted to their sodium derivatives by reaction with sodium amide, to obtain the compounds of the present invention.

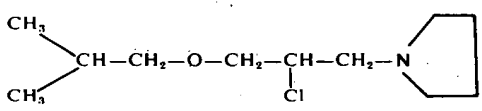
The invention also includes the addition salts of the compounds having the general formula I with pharmaceutically acceptable organic and inorganic acids such as hydrochloric acid and fumaric acid.

As an example of the process of the invention there will now be described the synthesis of 1-(3-isobutoxy-2-(phenylbenzyl)-amino)-propyl-pyrrolidino-hydrochloride (Compound No. 1).



First step

Preparation of 1-(3-isobutoxy-2-chloro)propyl pyrrolidine



345 ml of thionyl chloride dissolved in 345 ml of chloroform are added, drop by drop, to 275 g of 1(3-isobutoxy-2-hydroxy)-propyl-pyrrolidine dissolved in 350 ml of chloroform, while maintaining the temperature at approximately 45°C. The reaction mixture is heated to reflux until gas is no longer evolved. The chloroform and the excess of thionyl chloride are removed under reduced pressure. The residue is poured on to 400 g of crushed ice. The reaction mixture is rendered alkaline with soda and the resulting mixture is extracted twice with 250 ml of diethyl ether. The combined ethereal extracts are dried over anhydrous sodium sulphate. After evaporation of the solvent the residue is distilled under reduced pressure: 220 g of product are obtained having the following properties:

Boiling point = 96°C/3 mm, $n_D^{24°C} = 1,4575$,

Second step

Main product

ml of diethyl ether. After the ether has been evaporated, the residue is distilled under reduced pressure and has Bpt = 184°C/0.1 mm, $n_D^{20} = 1.5538$.

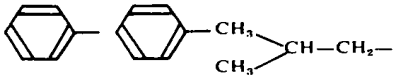
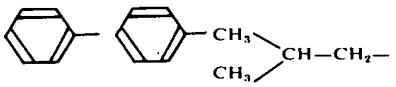
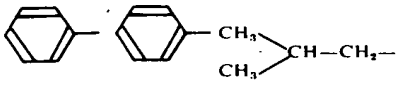
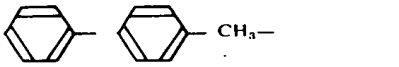
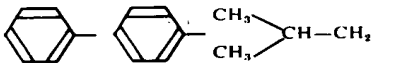
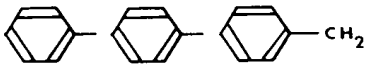
77 g of the pure base in the form of a viscous liquid is thus obtained.

The hydrochloride, which is prepared in conventional manner, has a melting point of 128°C.

Analysis	C%	H%	N%
Calculated:	71.52	8.75	6.95
Found:	71.20	9.01	6.93

Table I which follows sets out a series of products according to the present invention which were obtained using the foregoing method but substituting the appropriate intermediates containing the desired groups R and A and Ar and Ar' respectively.

TABLE I

COMPOUND No.	Ar	Ar'	R	A	Melting Points of Salts °C	ANALYSIS C% Theory	C% Found	H% Theory	H% Found	N% Theory	N% Found
1					Hydrochloride 128°	71.52	71.20	8.75	9.01	6.95	6.93
2					Fumarate 150°	67.08	66.90	7.66	7.20	8.69	8.75
3					Fumarate 98°	69.39	69.46	8.31	8.34	5.77	5.72
4					Fumarate 155°	68.16	68.42	7.32	7.30	6.35	6.31
5					Fumarate 195°	67.44	67.90	7.68	7.76	5.61	5.64
6					Hydrochloride 133°	74.55	74.05	7.82	7.40	6.21	6.14

23.4 g of sodium amide is added little by little to a solution of 92 g of N-benzylaniline in 500 ml of anhydrous xylene. The reaction mixture is then heated at 130° to 135°C for 6 hours.

Whilst maintaining the temperature at 110°C, 110 g of the product of the first step dissolved in 150 ml of xylene is added and the product heated for 6 hours at 120°C.

The product having been allowed to cool to ambient temperature, 200 ml of cold water are added. The organic phase is separated and extracted with an aqueous solution of hydrochloric acid.

After twice washing with 100 ml of diethyl ether, the aqueous phase is made alkaline with 50% caustic soda solution. The liberated base is twice extracted with 150

The pharmacological activity of the compounds of the invention in the cardiovascular field was determined on the dog in the manner described below:

An incision is made in the right-hand chest wall of an animal, which has been anaesthetised with chloralose and given artificial respiration, to enable the blood from the venus sinus to be drawn off and the apparatus required to record the following parameters to be inserted in position:

a. Output of the coronary sinus;

b. P_bO_2 of the blood from the coronary sinus; and

c. Amplitude of the contractions of the right ventricule.

At the same there were also measured:

d. Arterial pressure in a main carotid artery: and

e. The rate of heart-beat determined cardiotachometrically.

Table II which follows records the determinations made of the various parameters, the results being expressed as a maximum percentage variation relative to the pre-treatment values.

TABLE II

COMPOUND No.	DOSE mg/kg. (intravenous)	NUMBER OF ANIMALS	CORONARY OUTPUT %	RATE OF HEART-BEAT %	SINUSAL P_aO_2 %	ARTERIAL PRESSURE %	AMPLITUDE OF VENTRICULAR CONTRACTION %
1	2.5	7	+51.2	−28.6	+119.2	−39.8	−0.7
	5	7	+36.9	−31.8	+120.8	−40.2	−22.3
2	5	3	+55	−28	+71	−43	−25.5
3	5	4	+117.8	−19.2	+158	−30.5	−3
4	5	4	+110.5	−14.5	−56	−26	+17.5
5	5	3	+24	−3.5	+11.6	−15	+1.5

These results show that, taken as a whole, the products under examination have the ability to increase the output of coronary blood, to reduce the rate of heart beat and especially, with the exception of compound No. 4, to increase the oxygen content of the venous cardiac blood. The latter action is demonstrated by an excess in the supply of oxygen relative to the requirements of the myocardium. The arterial pressure is also lowered for a short time. In most cases there is little alteration in the ventricular inotropism.

Particular note should be taken, in the case of compound No. 1, of the very considerable increase in the oxygen content of the venous cardiac blood in relation to the increase in coronary output, which may be simply attributed to the improved circulation of the blood. The extremely slow rate of heart-beat brought about by the products certainly plays an important role in this respect.

It then seemed interesting, using compound No. 1, to seek the existence of an action on the β-adrenergic receptors in the manner outlined below:

A stimulating electrode was placed in position on the right stellar ganglion of dogs anaesthetised as described above and for which there were recorded:

a. The arterial pressure,

b. Ventricular inotropism (the amplitude of contraction of the right ventricle), and

c. The rate of heart-beat.

The chest of the animals were not open and they were breathing freely.

The β-adrenergic receptors, both cardiac and vascular, were stimulated by electrical stimulation of the right stellar ganglion or by intravenous injection with isoprenaline (5 μg/kg). The measurements were taken both before and after administration of compound No. 1 by the intravenous route in a dose of 5 mg/kg bodyweight.

The following Table III gives the average percentage inhibition of the cardiovascular effects of isoprenaline and of the cardiac effects of the stimulation of the right stellar ganglion.

TABLE III

	Number of animals	PERCENTAGE INHIBITION OF Hypotension	Rate of Heart-beat	Positive inotropic effect
ISOPRENALINE (5 ug/kg Intravenous)	4	−54%	−32.7%	−46.5%
STIMULATION OF THE RIGHT STELLAR GANGLION	3		−30%	−21.3%

These results show that a partial inhibiting effect is achieved as regards the β-adrenergic receptors at the cardiovascular level of treatment.

In conclusion, it is apparent that the members of the series of compounds possess a distinct cardio-vascular activity which is manifested by an improvement in circulation by the enhanced oxygenation of the myocardium in consequence of a slow rate of heart-beat.

In addition to the general properties of the compounds of the present invention, compound No. 1 is also of interest in that it also possesses inhibiting effects with respect to the stimulation of the β-adrenergic receptors.

The pharmacological activities of the compounds having the general formula I thus enable their application in human therapy to be anticipated, as medicaments intended for treating particularly:

Myocardiac anoxaemia,

Coronary deficiencies, angina pectoris,

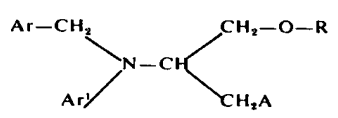
Infarction of the myocardium, and

Cardiac deficiencies associated with coronary circulatary trouble.

When admixed with the usual excipients, they may be administered orally or rectally, in daily doses of between 100 and 800 mg.

What we claim is:

1. An ether of n-propanolamine having the formula



wherein A is morpholino, pyrrolidino, piperidyl, and di-lower-alkyl amino, R is a straight or branched chain lower alkyl, or benzyl, Ar is aryl and Ar^1 is aryl or pyridyl, and pharmacologically acceptable salts thereof.

2. The ether of claim 1 in which A is pyrrolidino, R is isobutyl and Ar and Ar' are both phenyl, and the hydrochloride thereof.

3. The ether of claim 1 in which A is pyrrolidino, R is isobutyl, Ar is phenyl and Ar' is 2-pyridyl, and the acid fumarate thereof.

4. The ether of claim 1 in which A is diethylamino, R is an isobutyl and Ar and Ar' are both phenyl, and the acid fumarate thereof.

5. The ether of claim 1 in which A is morpholino, R is isobutyl and Ar and Ar' are both phenyl and the acid fumarate thereof.

6. The ether of claim 1 in which A is piperidyl, R is benzyl and Ar and Ar' are both phenyl and the hydrochloride thereof.

* * * * *